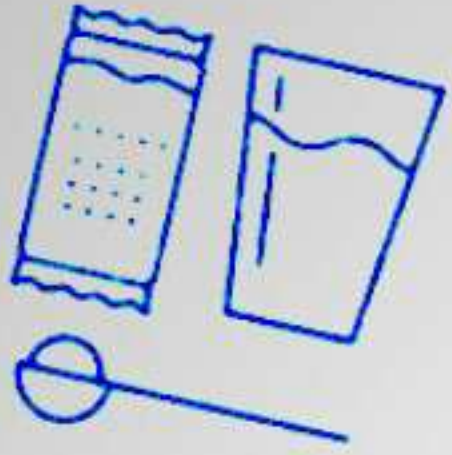
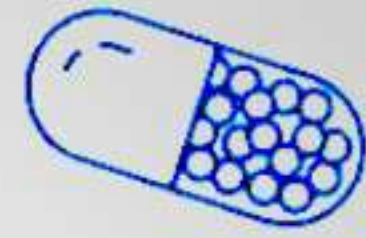
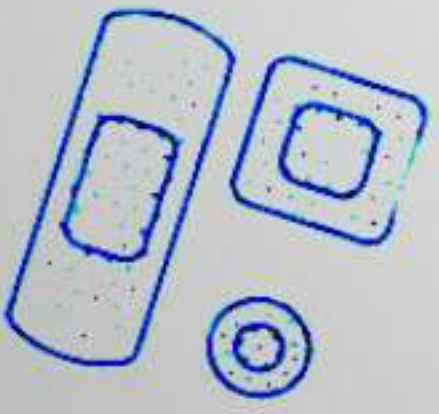




Dr. A.M Fouada
Lectures

ANS
GIT



VISIT...

LANZAROTE
Caliente.COM

- ANS :- it's the division of the nerves sys. concerned with regulation of autonomic functions.

- It's divisions :- a) sympathetic b) parasympathetic

- system :- 1. higher center 2. Nerves 3. chemical transmitters 4. Receptor

* High centers :- a) Medulla b) hypothalamus c) Reticular formation
d) Cortex

Most internal organs are "dual supply" [sympathetic & parasympathetic]

Autonomic nerve supply relay to (ganglia) : collection of neurons & ganglia → control (+ or - the signals)

In parasympathetic the ganglia ⇒ close to organ

In sympathetic " " ⇒ paravertebral

The drugs may work in :- ① nerve ending (s or p)
② Receptors ③ parasympathetic ganglia

→ Most organs receive dual supply : in some case one of them takes the overhand from the other or they may equalize
e.g. : (sym : 50 - para 50), (sym. : 80 - para : 20), etc.

→ Some Organs receive single supply as :- ① suprarenal gland
② sweat gland ③ B.Vs

The organs do not have all types of receptors but mostly there are One receptor "pre-dominant"

NAChR :- The fastest receptor that can response to ACh.

Cholinergic receptors :- M receptors : M₁, 2, 3

Adrenergic receptors :- α₁, α₂, β₁, β₂, β₃

More than 99% of the receptors presence inside the heart :- β₁

→ Bradycardia (para-)

++ :- Block M₂ receptor
• activate β receptor

⇒ Tachycardia (symo)

++ :- Block β₁ receptor
• activate M₂ receptor

Q :- How can we control the Autonomic system?

1. higher center 2. Nerve ending 3. Receptor (more selective)

Ex :- 1. 2. 3. ganglion blockers 1. 2. 3. non-selective = non-specific

Fate of transmitter :- breakdown by cholinesterase enz. (ChE)

→ ChE :- 1) true (acetyl ChE) → specific (just breaks ACh)

2) pseudo (butyl ChE) → non-specific (breaks ACh + heroin cocaine, ... etc. [its presence in Liver, plasma])

⇒ true :- CNs, RBCs + essential for life unlike pseudo

- Fate of catecholamine (epinephrine + nor-epinephrine) :- reuptake 80% , 20% → breaks by MAO enz. + COMT

Reserpine drug :- MoA :-

يقلل NA من الدخول إلى vessels وبالتالي يتركز في السيتوبلازم و يتأكسد بواسطة

① metanephrine ② VMA -> MAO & COMT enz. لا يتحول كالمعتاد

→ Normal ring of catecholamine in the blood :- 10 ng/L

* the stress ↑ this ring $1 \times 10 \Rightarrow 100 \text{ ng/L}$.

* Adrenaline ampule (inj.) $\Rightarrow$ ↑ the ring to 100 ng/L

* pheochromocytoma (suprarenal gland tumor)

pheochromocytoma :- unilateral tumor [in 90% of cases it's benign] & it's origin $\Rightarrow$ anterogranular cells.

nACh receptors :- a) neural $\rightarrow$ ganglia b) muscular $\rightarrow$ muscles

(a + b) are Ion channel, they differ from the other receptors in the tissue (M_1, M_2, M_3) in structure & function.

The 3rd division of ANS is :- ENS of intestine * (mcq)

$\Rightarrow$ NANC (non-adrenergic non-cholinergic) transmitters :- ATP - purines

Angiotensin - histamine - serotonin - NO - etc -

it's receptors $\rightarrow$ regulation function to 1st transmitter (ACh)

* Adrenergic receptors :-

كل ال adrenergic receptors ال G protein و هي من عائلة ال receptors

فهي تنقسم إلى 3 أنواع 1- stimulatory 2- Inhibitory 3- Gq

1- stimulatory 2- Inhibitory 3- Gq

Types of adrenergic receptors :-

① α_1 :- (ABC) subdivide

a - Blood vessels :- if st $\rightarrow$ V.C [Precisely α_{1A}]

b - Uterus :- contraction "apportion" لا ينقبض إلا بحالة "apportion"

c - eye :- mydriasis (α_1)

d - Urinary & GIT :-

1- wall $\rightarrow$ relaxation

2- sphincter $\rightarrow$ contraction ($\alpha_1, \alpha_2, \alpha_D$)

e - sweat gland :- In for head & palm

α_2 :- ABC subdivide

- mostly in presynaptic (nerve terminal)
- nerve terminal regulation
- α_2 always opposite α_1 and it's always inhibitory $\downarrow$ NA

B_1 :- Cardiac B_1 :-

1. $\uparrow$ all cardiac properties : HR, contractility, ... etc
* إذا جاء المريض وكان يشتكي من خبط في النبض أو Tachycardia فإنه يكون السبب هو B_1 ، والحد الأقصى هو أن يعطى B_1 blockers
2. Kidney : secrete Renin
3. Lipocyte $\leftrightarrow$ adipocyte { كلن بكيان قليلة لأن الـ B_3 overhand
مذكوره لاحقاً الـ B_3 }

B_2 :-

- في حالة الخطر تساعد على الجري وأثناء الجري تحتاج الـ $SK.m$: تقوّم الـ B_2 بعمل V.D الـ skin vessels حتى يكثر الدم في العضلة ويسهل ذلك عملية الجري وآلية ذلك كالتالي :- B_2 تحفز استجابة الـ nAChR الـ ACh بشكل أفضل من المعتاد أي أنها تقوّم بعمل facilitation في الـ neuro muscular transmission
- $\leftarrow$ أيضاً تقوّم B_2 بإدخال K^+ إلى العضلات $\leftarrow$ action potential وهذا يسبب انقباض العضلات بسهولة ودون أية مشاكل لكن خلال ذلك يحدث نقص في نسبة الـ K^+ في الدم $\leftarrow$ hypokalemia (SE)

shortly :-

1. V.D of SK.m (blood vessels).
2. Facilitation of neuromuscular transmission.
3. $\uparrow$ the storage of K^+ inside the muscle from the blood.
4. $\uparrow$ glucose in Blood from the Liver.
5. Bronchodilatation.
6. Secreat aqueous humour.
7. Relaxation of uterus during dangerous to avoid apportion.

N.B $\leftarrow$ تقريباً كل وظائف B_2 مفيدة عدا واحدة أي أنها يمكن أن تسبب Tremor أثناء قيامها بالـ facilitation

B_3 :-

$\leftarrow$ نستطيع القول بأن B_3 هي نوع من B_2 !! وهي موجودة بشكل كبير في الـ adipose tissue ولذا نشغل الـ Lipolysis

N.B :- لا يوجد B_3 agonist ~~تحت~~ $\leftarrow$ because it doesn't uniformly distributed all over the body.

* Adrenergic receptor :-

- أي دواء يحفز ($\alpha_1, \alpha_2, \beta_1, \beta_2, \beta_3$) نسميه : sympathomimetic سواء
قام بتحفيزها بشكل كامل أو بعض منها فقط ...

Sympathomimetic :-

1. MOA :- [a] Direct :- n. ending α في الـ n. ending
بشكل مباشر ونسميه Direct sympathomimetic
[b] Indirect :-
* إذا كان عمله : release for NA from n. ending أو أن قام بتعطيل الـ MAO enz.
نسميه Indirect sympathomimetic

* Chemical :-

- [A] Catecholamine :- 1 - not absorbed orally 2 - Can pass BBB
3 - MAO & COMT 4 - short duration -
[B] Noncatecholamine.

* Drugs :-

▣ prototype :- the most important drug of all family is :-

Adrenaline = (Epinephrine) :-

- it's the chemical transmitter inside the sympathetic sys.
- Origin :- suprarenal gland → (natural)

→ Chemical :-

- 1 - Natural catecholamine 2 - Contain catechol ring.

→ pharmacokinetics :-

- a - absorption :- ① not orally absorption ② skin absorption sluggish "few" → VC
③ ophthalmic absorption (could be but rare) ④ Inhalation

- b - Distribution :- ① Can pass BBB so it doesn't reach to CNS

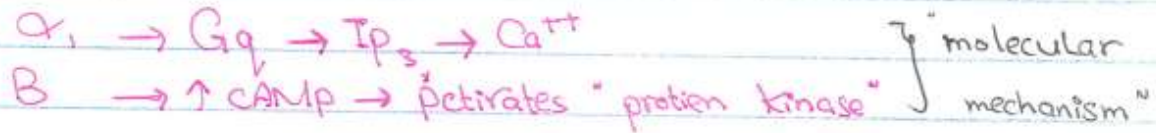
- c - Metabolism :- يتكسر بواسطة الـ MAO & COMT enz. ويتم ذلك خلال دقائق

- d - Excretion :- a) metanephrine b) VMA

حقنة الأدرينالين تؤخذ SC أو تحت IN وفي حالات IV تكون هناك
خطر كبير لأنها قد تسبب مشاكل في القلب ← Ventricular fibrillation

* MOA :-

* تأثير الـ adrenaline على كل من α_1 و α_2 receptors على الـ α_2 receptors
 "presynaptic" لذلك لا يستطيع الوصول إليها أي شيء
 و تكون كافية للوصول إليها في الـ (presynaptic)



الـ adrenaline آلية عمل الـ

* Effects :-

[1] Blood pressure :- according to dose !!

$\rightarrow$ Ampule or $\frac{1}{2} \rightarrow \uparrow$ systole , $\downarrow$ diastole

$\rightarrow$ more than therapeutic dose :- (large dose) :- $\uparrow$ systole , $\uparrow$ diastole * why?

* because $\alpha \Rightarrow$ (predominant) $\rightarrow$ generalize the v.c $\rightarrow \uparrow$ diastolic Bp.

[2] Heart :- ① $\uparrow$ HR $\uparrow$ contractility ② arrhythmia (VF)

[3] bronchi $\rightarrow B_2 \rightarrow$ Bronchodilation

[4] CNs $\rightarrow$ No effect because it does not pass BBB !

[5] eye $\rightarrow B_2 \rightarrow$ secrete aqueous humour - in case of Glaucoma.

* Uses :- in emergency :-

[1] Acute anaphylactic shock * the best route of administration of Ad. in case of Anaphylactic shock ? I.M

[2] Acute bronchospasm.

[3] Cardiac arrest.

[4] Local anesthesia $\Rightarrow$ v.c $\Rightarrow \downarrow$ Bleeding + long duration of local anesthesia ...

* SE :-

1. ↑↑ hypertension → cerebral hemorrhage
2. Tremors
3. Tachycardia → arrhythmia → V.F
4. Acute heart failure
5. " pulmonary edema
6. gangrene of fingers.

Q:- The most dangerous adverse effect of epinephrine injection is?
arrhythmia & V.F

* Contraindication :-

1. Hypertension
2. Cardiovascular problems
3. Large dose with local anaesthesia
4. Cardiac outflow obstruction (CoO)
5. Hyperthyroidism (sympathetic over activity)

✱ Direct acting sympathomimetics

2. NA
3. Dopamine
4. B₂ agonist → selective
non-"
5. Doputamine
6. α agonist
7. Dopamine receptor agonist ...

(2) NA :-  :-

1. catecholamine
2. not absorbed orally
3. does not pass BBB
4. Not exposure to air

→ NA :-

[α₁, α₂, α₃] but 90% ⇒ (α₁) ⇒ V.C → the main effect of epinephrine vs.

- B₁ :- 10% ⇒ NA when given → α₁, B₁ "short"

- very short acting

Uses :-

- 1- V.C (acute hypotension state)!
- 2- we don't give it injection direct, ~~SC~~, Orally → The only route is :- Intravenous infusion! **Q:- why?**
 → answer :- VC → tissue necrosis!!
 ← جزء نفيس الضغط للمريض أثناء إعطاء الحقنة! لا تخاف أن تشرب بـ ↑ Bp
 ← مجاعة و جوع شديدة ← * cerebral hemorrhage *
3. Baroreflex → (vagus n.) :-
 reflex bradycardia : يسبب ↑↑ الضغط فجأة يرسل إلى الدماغ ويقفز بقل : reflex
 → Atropine :- stop this reflex!

[3] Dopamine :-



→ Dopamine :- (Ampule) :- it's differ from the NA, A
 ← في خلاف هذا هو إلى الـ « Dopamine » يتصلب في الوريد إذا لم يمتزج بالـ saline

① Low dose → D_1 :- in renal vasculature → ↑ urine output.
 ↳ mesenteric Bv

② Intermediate dose → B_1 → CO ↑

③ high dose → α_1 → V.C → ↑ Bp.

Shock :- ↓↓ Bp, tissue perfusion :-

Q :- with shocked pt., what's your goal of therapy?

A: shocked state means: hypotension associated with impairment of tissue perfusion → my goal of therapy is :- to restore perfusion first then hypotension ..

[4] Dobutamine :-

- Dopamine

- Dobutamine

- Not catecholamine, comes from Dopa
- D_1, B_1, α_1
- shock: syptic shock (specially)

- synth. Cat.
- B_1 only
- ↑ HR, CO
- shock: cardiogenic

* β_2 agonists :- β

1) β_2 :-

Selective β_2 agonist :-

Drugs :-

- | | |
|----------------|--------------|
| 1- Salbutamol | 4- salmetrol |
| 2- Ritodrine | 5- formotrol |
| 3- Turbutamine | 6- bumbetrol |

β_1 :-

Dobutamine



Cardiogenic shock

β_1, β_2

"non-selective"

* non-catecholamine :-

- it could be given orally
- absorbed - pass BBB
- Long duration
- doesn't destroyed by MAO & COMT

* effects :-

- 1) $\beta_{2,vs}$:- V.D in skin & coronary a.
- 2) uterus : Relaxation
- 3) Tremors of the hand
- 4) Lung $\rightarrow$ bronchodilatation

* Uses :

$\rightarrow$ Bronchodilatation

1. Bronchial asthma
2. Uterine relaxation during pregnancy $\rightarrow$ Ritodrine

* Adverse effect :-

- T $\rightarrow$ Tachycardia + arrhythmia
- T $\rightarrow$ Tremors
- T $\rightarrow$ Tolerance
- H $\rightarrow$ Hypokalemia

* # α_1 or α_2 : "أدوية لها تأثير على الأوعية الدموية"

1) Alpha agonist :- * phenylephrine * methoxamine * midodrine :-

- a- non-catecholamine drugs ... etc.
- b- Relatively long duration (stim. of $\alpha_1 \rightarrow$ v.c)
- c- use them when we want to $\uparrow$ Bp + VC
- d- eye drops, injection, nasal drops

[2] Xylometazoline, Oxymetazoline :-

→ non selective (stim. α_1 (α_2))

!! α_2 $\leftarrow$ ينظم تأثيرها إذا استعملت بتركيز عالٍ

Nasal decongestant + eye drop :- أكثر استعمالها $\leftarrow \alpha_1 \leftarrow V.C$

* Adverse effects :-

① precautions of nasal decongestant :-

- Rebound (minimal dose)

- V.C $\uparrow \uparrow$ systemic hypertension $\rightarrow$ stroke

- V.C $\rightarrow$ Atrophic Rhinitis
" mucosa

يُسبب لفتره أطول
من ٢ أسابيع ...

(α_2 agonist) :-

① Clonidine :-

- stim. $\alpha_2 \rightarrow$ ① $\downarrow$ central sympathetic outflow $\rightarrow \downarrow Bp$

② $\downarrow$ RBF (Renal blood flow)

③ $\downarrow$ GFR

④ drug addiction (حبس)

* Adverse effect (SE) :-

- S $\rightarrow$ sedation, dry mouth

- S $\rightarrow$ sudden with alcohol

- S $\rightarrow$ severe hypertensive

- S $\rightarrow$ salt & water retention

② Tizanidine :-

① = stim α_2 in spinal cord just 1 $\rightarrow$ muscle relaxation

* use RL in «Muscle spasm»

② Multiple Sclerosis :- * (مرض التصلب المتعدد)

Q: Drug use to relax the skin in painful static conditions?

$\Rightarrow$ Tizanidine .

③ Fenoldopam :-

1- catecholamine (synthetic)

2- Not absorbed orally

3- don't pass BBB

4- must given parenteral

5- short duration

6- stim. D_1 just

7. Used as I.v injection in emergency cases

* SE :- $\uparrow$ IOP

glaucoma. $\leftarrow$ (IOP) $\leftarrow$ $\uparrow$ systemic $\leftarrow$ ($\downarrow Bp$) $\leftarrow$ هذا

Sympathomimatic drugs :-

A. Direct :-

1) Amphetamine :-

- indirect acting sympathomimetic drug
- synthetic (not natural) , non-catecholamine , can pass BBB + CNS

* SE :-

- 1- CN ++
- 2- Anorexia
- 3- euphoria
- 4- Hallucination
- 5- Addiction

* Contra indication :-

- 1) CN's stimulant
- 2) obesity

تم منع هذا الدواء عن السوق ومكتسب له نوع من أنواع المخدرات

* Derivative drugs :-

- 1- Methyl phenylet

use in "ADHD"

⇒ Modafinil

"Narcolepsy"

* SE :- * in high dose *

- 1- insomnia
- 2- tachycardia
- 3- nervousness
- 4- headache
- 5- seizure → (dangerous for pt. with epilepsy disease)
- 6- physical dependence →

2- Cocaine :- - alkaloid nature → coca plant !

- It has same effects of : amphetamine *
- Local anesthetic "eye drop"
- If toxicity → adverse effect same to amphetamine
- we gave this pt. ⇒ Benzodiazepine

* → Mixed acting sympathomimetic :- * Ephedrine *

→ Direct : β_1, α

→ Indirect : Releases for NA

[use very minimal]



- alkaloid (natural)
- Non-catecholamine



1) Stim. all receptors α, β

2) Release NA from the Nerve ending

3) CN +++

كافي يستعمل على أساس أنه يقوم بتحفيز β_2 في حالة : Bronchial asthma

لأنه يحفز β_2 فيلنا (BD)

كافي يستعمل أيضاً لعلاج : التبول اللاإرادي عند الأطفال

س/ لماذا لم يُقدِّم دواء الـ ephedrine يستعمل ؟

because it's :- ① non-selective sympathomimetic + mixed

② Urine Retention (specially in enlargement prostate)

س/ لماذا لا يؤخذ orally ويستعمل في الجسم حالي 8h وينتج receptors α, β

في الـ wall Relaxation ← و في الـ sphincter Contraction

والتالي يسبب تضيق المسالك للبول

س/ Adrenaline يتناول α, β لماذا لم نقل أنه يسبب هذه الأعراض ؟

ج/ لأن إقامته في الجسم يستمر لدقائق فقط !

→ Alpha adrenergic blockers

Baroreflexes :-

Note : sudden rise of Bp → RB "reflex bradycardia"

• " drop of Bp → RT "reflex tachycardia"

إذا صاحف إزته الدواء هو المسبب في sudden change يكون له تأثير على القلب

مثلاً :- stim. B receptor .. ، الـ reflexes هذه لا تظهر .

الأدرينالين Adrenaline يسبب Bradycardia

B blocker ← Bp ↓ هل تسبب RT ؟

ج/ لا ، لأن القلب عندما يتخفف تقوم الـ stretch receptor بإرسال إشارة إلى brain

حتى تقوم بقل (RT) ، ونهض هذه الإشارة من الـ brain لكن زوال B blocker تكون

مقابلة الـ receptor فلا يحدث (RT) !!

* α adrenergic adreno blockers :- 4 families :-

① $\alpha_1 + \alpha_2$ (non-selective) : phenoxybenzamine

② α_1 (selective α_1 blockers) : phentolamine

③ α_2 (" α_2 ") : prazosine

④ Ergotalkalout : yohimbine

Drugs :-

-1- phenoxybenzamine :-

• long duration

• block $\alpha_1 - \alpha_2$ (irreversible)

• it takes (4 days)

بحسب قاتل الـ receptors لمدة 4 أيام

يسبب hypotension لأنه يقلل الـ α ، ولأنه يقلل حدة تسبب من الـ VC

← Bressure ↓ ، وهذا يكون مصحوب بـ [Tachycardia Reflex

الرواء :- Bp + RT

Uses of phenoxybenzamine :- long duration *

1- pheochromocytoma $\Rightarrow$ tumor in the supra renal gland :-

- * it's usually unilateral, benign, cause : $\uparrow\uparrow$ Adrenaline secretion
- * Increases "Adrenaline" in the blood :- a) palpitation b) Tachycardia c) arrhythmia ... etc.

Treatment :- 1) surgical 2) Block α & β together

* لا يجب إعطاء أدوية α لفرد بها حالة الـ pheochromocytoma لأنها بذلك ستلحق قتلنا α فقط فنقوم α β بل تأثيراتها الجانبية مثل الـ Tachycardia, Tremors, arrhythmia لذلك نستخدم هذه الحالة نعطى α + دواء آخر "propranolol" لأنه يعتبر β blocker يقطع كل β_1, β_2 مزبونها...
سأعطى أدوية β بمفردها؟ ولماذا؟!

ج/ لا، لأن α يقل "severe V.C" وقد يسبب cerebral hemorrhage
سأعطى أدوية α و β مع بعضها، تكون الأولوية لـ β ؟

ج/ يجب أن يتناول المريض أدوية β blocker أولاً، لأن المشكلة الرئيسية التي نرغب بعلاجها هي الـ hypertension، فبدلاً من الأدوية التي تؤمن هذه المشكلة ثم β blockers

Adverse effects :-

- 1- $\downarrow$ Bp + RT
- 2- Failure of ejaculation
- 3- myosis

Selective α_1 blockers:-

prazosin :- Doxazosine Tamolocin indoramine

- $\rightarrow$ it's blocks α_1 just - الـ α_1 receptors في الـ smooth muscle ويقل
- $\rightarrow$ no V.C $\Rightarrow \downarrow$ Bp direct relaxation أي تأثير مباشر ليس له علاقة بالـ receptor
- $\leftarrow$ لأن الدواء عمل α_1 بطريقتين $\rightarrow$ 1/ يقل α receptor و 2/ يقل V.C
- 3/ $\leftarrow$ direct relaxation في الـ smooth muscle

* any α blocker cause $\rightarrow \downarrow$ Bp + RT (weak) because :-

- a- non-selective : Tachycardia $\rightarrow$ + reflex (under effect of $\uparrow$ NA)
- b- selective : $\downarrow$ Bp + RT but no $\uparrow$ (NA) $\Rightarrow$ Tachycardia (weak)

shortly :-

- ① $\downarrow$ Bp with no RT.
- ② $\downarrow$ Bp with no effect on RBF, GFR.
- ③ $\downarrow$ Bp + $\downarrow$ Fat in blood.

2] Doxasin :-

→ The longest drug with (duration of action) about 22 h.

* (mcg)

* Uses :-

- 1- hypotension (specially with pt. with kidney problems)
- 2- Acute heart failure
- 3- enlargement prostate

Selective α_1 blocker :- $\Rightarrow$ arteriolar dilatation $\rightarrow$ $\downarrow$ venous return

Tamsulosin $\rightarrow$ selective on (prostate) : it blocks $\alpha_{1A}, \alpha_{1D} \Rightarrow$ + flow of urine without any change for Bp.

Adverse effect :-

- 1- first dose syncope :- مع أول جرعة يتناقص الضغط بشكل كبير ويحدث ذلك فجأة لذلك قد يفسى على المريض ويحدث له : (salt & water depletion) ويظهر التأثير خلال 7-10 دقائق ، لذلك نطلب من المريض أخذ جرعة صغيرة (بأقوى) ونزيد جرعة كل يوم
- 2- Fluid retention
- 3- False +ve test for antinuclear factor قد يحدث خطأ وتظن أن عند المريض *Rheumatoid arthritis* (RA)

yohimbine :

- alkaloid (plants)
- blocks α_2
- NA $\uparrow$ release

* Ergot alkaloids :

- Ergotamine
- Ergometrine
- Ergotoxine (very toxic)

* Semisynthetic :

- 1 $\rightarrow$ Dihydroergot (H group)
 - 2 $\rightarrow$ Methyl ergometrine (CH₃ group)
 - 3 $\rightarrow$ alhydroergotoxin
 - 4 $\rightarrow$ Bromocryptine
- } semi synthetic

* They all stim. vomiting center

* Caffeine $\Rightarrow$ $\uparrow$ absorption for these drugs.

Ergotamine	partial agonist ($\alpha, 5HT$)	V.C in cerebral B.v.s	migrain
Ergometrine	agonist α_1	V.C on vessele + spasm on uterus	نرف ppH بعد الولادة
Dihydro-ergotoxine	antagonist blocks α	C.V.D cerebral B.v.s	-cerebral insufficiency
Bromocryptine	من حبيبات : ① weak on α_1 (agonist & antagonist) ② stim. D receptor		

صداع نصفي

* Ergotamine : acute migraine attack

1/ يكون الـ B₁ في حالتها الطبيعية يقوم بحدوث لنا sudden release 5HT

وهذا يقل VC for cerebral vessels وهذا يقل VC

accumulation of worst products : وهذا يقل VC VC for cerebral vessels
headach severe VD ويبدأ الشخص يشكو من

يعتبر انه الدواء الوحيد الذي يستطيع إعادة الـ vessels إلى حالتها الطبيعية

يفضل أخذ الدواء مع القهوة حتى تزيد من كفاءة امتصاصه

نستخدم هذا الدواء كإجراء وقائي للصداع لأنه سيسبب الصداع للشخص -

يذهب الدواء الـ vessels يقوم بحدوث VC وهذه الآلية تشابه آلية الـ 5HT sudden release for

ويقوم الدواء بتجميع الـ worst metabolite products ويسبب الـ « headach »

Tryptane :-

[Symatreptan - Zolmetreptan - Naratreptan] → [expensive]

هذه العائلة تروج تشتغل على specific receptors في الدماغ مثل -

[5HT receptor type 1D, 1B]

↓ releas of inflammatory mediator عندما يشتغل الـ drug على هذه المستقبلات يسبب :

والـ metabolite إلى زيادة تطلع وتقل VD تشتغل وبالتالي الـ mediator إلى عامل pain

لا تستطيع الخروج وبالتالي يذهب الألم ، عندما يسبب الـ drug بـ B₁ يقوم بحدوث VC

وبالتالي تعود الـ vessels إلى حالتها الطبيعية .

ميزة هذا الدواء عن السابق أن له تأثير سريع جداً وتدخل في الـ acute stage

ومثال بيرة الناس تشعر بتحسن من أول جرعة (80%) ، ولكننا لا نستخدمه كوقاية prophylaxis

لنفس السبب الذي تم ذكره سابقاً ..

عندما ينسب هذا الدواء B₁ في الـ brain أحياناً ينسب أيضاً نفس الـ receptor

في الـ coronary a. ← receptor coronary VC وهذا قد يضر مرضى الـ ischemic disease

وأيضاً مرضى الـ angina (وهذا العيب لهذا الدواء) .

prophylaxis :-

1. propranolol (B blocker)

2. CCBs (calcium channel blockers)

3. TCA (Try cyclic antidepressant)

4. clonidine

* Ergometrine :-

in uterus $\rightarrow$ VC for spiral Bv_s (Bv_s of uterus)

② direct spasm in uterus

- Uses :-

← يصبح استخدامه في حالة الولادة (لأجل زيادة الطلق) ؟

Contraction for uterus & servix * لأنه يقوم بعمل

يمكنه يستحسن جداً إعطاؤه بعد الولادة (بعد خروج placenta)

لأنه ال Contraction تساعد على التخفيف من النزيف بعد الولادة ...

* Dihydroergotoxin :-

α blocker drug $\Rightarrow$ VD (specially in the brain)

Use:- Senile cerebral insufficiency $\rightarrow$ الدم لا يصل للدماغ بشكل كافٍ وبالتالي يسبب النسيان ، لذلك نستخدمه للمرضى الكبار في السن إذا كانوا يعانون من نسيان مسرور

* Bromocriptine :-

(Stim. D_{receptor}) :-

① hyper prolactinemia :- pituitary gland ينبه الدواء مستقبلات D₂ في الغدة النخامية
وهذا يسبب prolactine $\downarrow$ فنستخدمه لعلاج الحالات التالية :-

- Infertility - hyperprolactinemia - stoppage for lactation

② parkinson disease :-

عندما يقل ال Dopamine في الدماغ يقل وتديلاً في ال (basal ganglia)

يشبه الشخص بالشخص ذو أعراض المرض والحل : نعطي الشخص هذا Dopamine

لأنه BBB doesn't pass الأفضل أن نعطي دواء ال Bromocriptine

لأنه non-catecholamine وبالتالي يستطيع الدواء المرور من ال BBB

فإنه يقل بشكل كبير ال Dopamine وينبه D_{receptor} وهذا مفيد طريق ال parkinson dis.

* Adverse effect :-

1. N & V

2. V.C in finger & coronary a. $\Rightarrow$ gangren + chest pain

3. Apportion $\rightarrow$ لأننا لا نستطيع ضمان ال selectivity لأي دواء

Beta adrenergic ~~rebo~~ blockers :-

- II
- $B_1 + B_2 \rightarrow$ non selective e.g: - propranolol .
- Sotalol . - Timolol
 - $B_1 \rightarrow$ e.g: - Atenolol . - Bisoprolol . - Timolol . - Acetolol

B BB + DVD action (Beta blocker with direct VD action)

عندما نُعطى المريض BB فإننا نقول بفعل B_1, B_2 receptors، ومن المعروف أن B_2 receptors توجد في VD و $skin$ و $muscles$ ، وبهذا المريض بالشكوى من :-

* peripheral ischemia

* problems due to blood flow for muscle

وهذا لا يقتصر فقط على BB بل على جميع الأدوية من BB $\leftarrow BB + DVD$ action

* Drugs :-

- 1 Carvedilol 2 Diltiazem

* pharmacokinetics :-

$\rightarrow$ selectivity :- α_1 features :-

- 1- well absorbed 2- extensive 1st pass metabolism

$\rightarrow$ Kinetics :-

a-Lipophilic : propranolol

b-hydrophilic : atenolol

Lipophilic $\leftarrow$ يعني أن هذا الدواء يذوب في الدهون وبالتالي له خاصية يكون أفضل (شبه complete)

لكن المشكلة هي أنه عند دخوله للجسم ينتشر بشكل جيد جداً ويوصل إلى CNS وبالتالي يكون له تأثيرات

CNS effects لأنه من BBB لكن مشكلته هي أنه $metabolism$ لأنه يدخل للجسم

كونه $Lipid$ soluble وبالتالي يصل إلى $Kidney$ أيضاً فتخرج $excreted$

أي أنه له تأثير على $Liver$ ويقلل $metabolism$ حتى يحوله إلى $water$ soluble

وبالتالي هذا الدواء يكون له $half-life$ أطول ..

! (Long duration of action = long half-life) $\leftarrow$ hydrophilic

.. لأن الماء لا يمتصها بنفس سرعة الدهون

-hypo

- 1- propranolol
- 2- its absorption better than hydro abs.
- 3- reach $\rightarrow$ CNS
- 4- Extensive metabolism in Liver to be excreted to convert it to water soluble
- 5- Short duration of action
- 6- $\downarrow$ Multiple dose

hydro

- 1- Atenolol
- 2- Less abs. than hypo .
- 3- Does not reach CNS
- 4- Direct metabolism because it's water soluble
- 5- Long duration of action
- 6- Once/day

Carvedolol :- BB, non-selective
* antioxidant drug

Nebivolol :- The most selective BB

• VD $\Rightarrow$ secret No so we count it (BB with D₂D action)

- Uses :-

- 1- pt. with hypertension
- 2- IHD (ischemic heart disease) classic angina
- 3- S.V.T (supra ventricular tachycardia)
- 4- hyperthyroidism
- 5- Esophageal varix
- 6- Glaucoma
- 7- pheno
- 8- pheochromocytoma.

- Adverse effect :-

- 1 fatigue :- $\downarrow$ CO $\downarrow$ Blood $\rightarrow$ skin * most common
- 2 Bronchoconstriction $\rightarrow$ never given to bronchial asthma pt.
- 3 Bradycardia $\rightarrow$ may lead to heart block
- 4 $\uparrow$ prephal ischemia
- 5 Metabolic adverse effect :-

a- BB $\uparrow$ K in blood $\Rightarrow$ not good for Renal failure pt.

b- $\uparrow$ plasma lipids ($\uparrow$ C, $\uparrow$ TG)

6 D.M

7 CNS :- * Depression * nightmare * sexual dysfunction.

- Contraindication :- Absolute contraindication [Abs CI]

- 1 Bronchial asthma
- 2 Heart block
- 3 Prinzmetal angina
- 4 if the pt. use it for long time [no sudden stopping]

- Not good :-

- 1 HF
- 2 p.v.D (peripheral vascular disease)
- 3 D.M
- 4 athletic $\Rightarrow$ fatigue

Adrenergic neuron blockers :-

كل الأدوية التي تسفل العزل nerve ending

* Drugs :

① α -M dopa :- * synthetic

* **MOA** :- participate in NA synthase $\rightarrow$ as a false substrate instate of formation of Dopamine from the normal Dopa ...

Useful for pregnant women. * حتى انه يُعتبر أفضل خيار

* SE :-

لعلاج ال hypertension في النساء الحوامل

- Depression - nightmare - Extrapyramidal Manifestation
- Hemolytic anemia • Autoimmune hepatitis
- Salt & water retention

* قد يحدث بعض التورم في بعض الحالات إذا

تم إستخدامه لفترة طويلة ، وهناك بعض الأدوية [mild diuretic] ولذلك لا علاج المضاعفات الطبيعية ..

Reserpine :- NA , Dopamine , Serotonine

- ① $\downarrow$ Bp ② Depression ③ parkinsonism ④ hyper prolactinemia

$\Rightarrow$ Used for ttt :- mild & moderate hypertension

* لكنه ليس خيار الأول

• MOA :-

الآلية فائقة على أن ال NA التي خرجت لخل وخليفة ما ثم يتم سحبها reuptake
فقدوا بهذه الطريقة وبالتالي رجوعها إلى ال vessels وبالتالي تتراكم في ال cytoplasm
ويُسبب ال MAO !

* MAO inhibitor + Reserpine $\Rightarrow$ Acute hypertensive crises .

Ach places :-

- 1- nerve ending 2- sk.m 3- aut ganglia ...

* Cholinergic receptor :-

A- Nicotinic receptor [sk.m, ganglia, SRG]

M1	M2	M3	Nn	Nm.
- Gq	$\downarrow$ cAMP	Gq	ganglia	sk.m
- Excretory	- inhibitor	exitory		$\downarrow$ muscle contraction
- gastric	- Cardiac	1. Bow 2. Smooth m.		
	it may lead to bradycardia	3- any gland		
		4- eye $\rightarrow$ (myosis)		

* Drugs :-

M	N
- Carbachol	- Lobeline
- Bethanecol	- Nicotin
- Pilocarpine	

[1] Carbachol :-

- stim M+N
- no chE → long duration
- don't give systemic (local eye drop)

[2] Bethanecol :-

- 1- stim. M just mostly in gut, urinary (specially M3)
- * ↑ motility
- * open sphincters

لأنه هناك خطر قد يتسبب في تأثير M2 على القلب فينقبض

- 1- Bradycardia
- 2- not good for pt. with (Retention) ^{قصور} that organic obstruction

[3] Pilocarpine

muscarinic agonist

M3 ^{قصور} ^{قصور} ^{قصور}

- ↑↑↑ secretions
- Sjögren syndrome : Dryness of all body secretion.
- eye drop → myosis

* SE :

- D → Diarrhea
- U → Urination
- M → Miosis
- B → Bradycardia , bronchoconstriction
- L → Lacrimation
- E → Emesis = vomiting
- S → Salivation , skin twitches

* Contraindication :-

- Bronchial asthma (BA)
- Urine retention due to organic obstruction

3 M.G

• autoimmune disease.

• Neostigmine + Atropine ?!

↑ muscle contraction ← stim. N_m receptor ← ↑ACh ← neostigmine (نشط)
 to block unwanted muscarinic effect ← Atropine (نطفي)

pyridostigmine :-

• more selective

• long duration of action (5-6 h.)

Q:- Why [pyridostigmine] is preferred to M.G?

① more selective on muscular junction (without severe muscarinic effect)

② Long duration of action → (2 or 3 daily)

4 Edrophonia :

more selective (better than pyridostigmine)

لكن لديه عيب وهو أنه حين تم تعينه ركزوا على جطه (very selective) وبالتالي أصبح تفاعل
 يقتصر على motor end plate وهذا سبب أن الدواء يخرج بسرعة من الجسم ولا يستمر
 تأثيره لأكثر من 1-5 دقائق، لذلك لا يستخدم هذا الدواء لغرض العلاج وإنما التشخيص
 → cholinergic rise

5 Donepezil, Rivastigmine :-

→ block ChE

→ no prephal effects

→ Alzheimer disease

* Irreversible :- organophosphate

→ Insecticides

→ Nerve gases

↑ ACh :-

- Cardiovascular sys. : bradycardia, hypotension

- Respiratory sys. : ↓↓ ~~the~~ inhibited

- GIT : Diarrhea, urination

- eye : severe myosis

- S.K.m : sweating, twitches, salivation, lactation.

:-

A	B	C
air way suction	Breathing جهاز التنفس الصناعي	circulation - pulse (severe bradycardia) - Bp (very low)

Drugs :-

[1] Atropine (high dose) : Ampule 2 mg

تدبره لا يقبل كخمس دقائق ملاحظة ال pulse , Bp ويحل اكر يفقدت المراقبة عن ساعة

[2] Oxime : - pralidoxime (PAM)

- diacytymonoxime (DAM)

] CHE reactivator

→ given parenteral I-v diffusion

[3] Diazepam.

First lecture... [GIT]

١٥/١٢/٢٠٢٠

- Peptic ulcer include
 - ulcer in stomach which called Gastric ulcer
 - ulcer in duodenum which called duodenal ulcer

- Peptic ulcer occurs when there is imbalance between the invasive and defence mechanisms
- Any defect ~~cause~~ in the defence force or increased in the invasive force causes ulcer.

The invasive forces

- * HCl
- * Pepsin
- * NSAIDs
- * Smoking
- * H. Pylori

The Defence forces

- * mucus coat.
- * Bicarbonate
- * Good Blood flow.

- Note \ Ischemia in the mucosa of the stomach may cause Peptic ulcer.

- The mucosa of the stomach is lined By \

- ① ^{Parietal} Peptic cells → Secrete HCl.
- ② Chief cells → Secrete Pepsin.
- ③ G cells → Secrete Gastrin [In stomach, duodenum, pancreas]
- ④ Enterochromaffin cells → Secrete histamine

* histamine is the main stimulant of parietal cell to Secrete HCl.

* Parietal cells have 4 Receptors in their walls \

- M_1 receptor, G_i receptor, H_2 receptor $\Rightarrow$

Stimulation of these $\uparrow$ Secretion of HCl.

- PG receptor $\Rightarrow$

Stimulation of it inhibits the HCl secretion

1) M_1 Receptor :-

- Stimulated By the action of acetylcholin under the effect of Vagal Tone.

* Note Ach stimulate also G_i cell to secrete Gastrin and enterochromaffin cell to secrete histamine

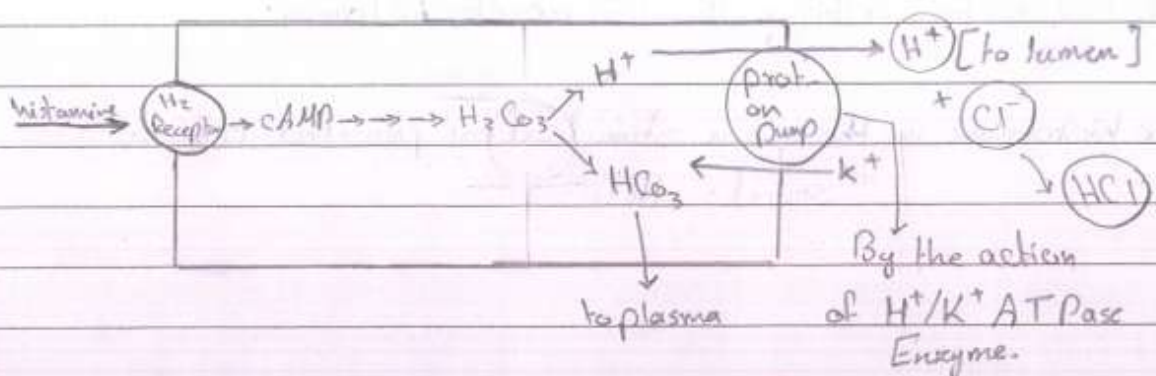
2) G_i Receptor :-

- Stimulated By Gastrin which is secreted under the effect of Ach stimulation on G_i cells.

3) H_2 receptor :-

- Stimulated By histamine which is secreted under the effect of Ach stimulation on enterochromaffin cells.

* Mechanism of formation of HCl under the effect of histamin stimulation \



4) PGI₂ receptor 2-

- Stimulated By PGE₂ $\Rightarrow$ Decreasing the formation of HCl and producing thick mucus coat also cause V.D leading to increase Blood flow to the stomach.

* Mechanisms of decrease the Secretion of HCl \

- ① Block M₃ receptors
- ② Block G₁₂ receptors $\Rightarrow$ "most minimal effect"
- ③ Block H₂ receptors $\Rightarrow$ "the final pathway, very effective"
- ④ PGI₂ analogue
- ⑤ Protein Pump inhibitors $\Rightarrow$ "The most effective drugs"

* H. pylori *

- * Mainly found in the antrum, It hides Between the mucosal layer of the stomach and the mucus coat.

- * It Secrete proteolytic enzymes causing chronic Gastritis which may develop into ulcer.

- * Detected By urea breath test.

- 50% of patients with H. pylori don't suffer from ulcer.
only 10% of them may have ulcer.

* Signs of P.U \

- mainly Epigastric pain.

- Cardiac if P.U is at the site of the heart.
- Cardiac if the pain is at the site of the heart.
- and if the pain is at the site of the heart.
- musculoskeletal if the pain is at the site of the heart.

* Difference Between GU and DU \

GU

- Diffuse pain
- May increase with eating & mostly "

DU

- Localized pain & point tenderness
- Some times the pain decrease after eating.

* The size of most ulcers is 1-2 cm, If it is more than 2, It is called **Giant Ulcer** and It need surgery.

* Treatment \

- First the non pharmacological treatment.

① Avoid the 3 S's

Smoking, Stress, Spices and fried food.

تجنب التدخين، التوتر، التوابل والأطعمة المقلية

② Stop the NSAIDs

* كلام لا يجان من تخفيف ألم المفاصل

Second the pharmaceutical treatment \

① Neutralization of HCl = Antacids

② Anti-Secretory of HCl

- Block M_1 receptor
- Block M_2 receptor
- Proton pump inhibitors

③ Mucosal Defence Mechanism

- Sucralfate
- Bismuth Subsalicylate
- Carboxenated
- IG analog.

④ *H. pylori* treatment.

First Neutralizing HCl = Antacids \ [Symptomatic relief]

① Na-Bicarbonate:

- * The fastest in action.
- * It can be absorbed and reach the systemic circulation →
- lead to ↑ Sodium in the blood causing
- By that salt and water retention and systemic alkalosis.

- **CI** \ In hypotensive patients.

② Ca-Carbonate:

- * 50% of it will be absorbed and ↑ calcium level in the systemic circulation
- * This may lead to Ca-stone formation.
- * If the dose was high, it will stimulate Gastrin secretion
- * Also cause Rebound hyperacidity.

③ Mg and Al-Salts:

- * Not absorbed 100% act locally.
- * But these salts will retain in the GIT and cause:
- Mg → Diarrhea.
- Al → Constipation.

- General Adverse effects of Antacids :-

* Change in Bowl habits [close to Mg, Al actions]

* May cause Rebound hyperacidity.

* Lead to cation overload :-

1] Na $\Rightarrow$ Salt and water retention

2] Ca $\Rightarrow$ $\uparrow$ Ca $\Rightarrow$ Ca stones

3] Mg $\Rightarrow$ $\uparrow$ Mg, muscle fatigue $\Rightarrow$ مقاومة في العضلات
 مقاومة في العضلات Mg is related

* Formation of chemical complexes with other drugs [chelation] $\Rightarrow$

هذا يعني ان الأدوية
 لا تتحرك في الدم
 لا تتحرك في الدم

- Second Anti-Secretory drugs \

① M₁ Blocker :-

- Like $\Rightarrow$ Pirenzepine

* Not very effective

* If the dose was high it may lose its selectivity and decrease the motility so much decreasing B₁₂ that the time of emptying $\Rightarrow$ Lead to $\uparrow$ HCl.

② H₂ Blocker :-

- Like $\Rightarrow$ Cimetidine, Ranitidine, Famotidine and Nizatidine.

* $\downarrow$ HCl B₁₂ 70 %

* Clinical uses :- ① All types of ulcers

② with NSAIDs.

③ Zollinger-Ellison Syndrome.

- Zollinger-Ellison Syndrome Is a tumor of the
G-cells in pancreas $\rightarrow$ lead to increase
Gastrin secretion $\rightarrow$ $\uparrow$ HCl.

* Side Effects \

① Cimetidine $\rightarrow$ has ① Anticarcinogenic Side Effects.

- Anticarcinogenic effects include Gynecomastia, $\downarrow$ Sperm count,
Galactosuria, $\uparrow$ prolactin & endocrinal S.E. "

Causes drug interaction $\leftarrow$ ② Inhibition of liver metabolism
By Cytochrome P₄₅₀

③ Reversible hepatitis and Bone
marrow depression

④ CNS effect $\Rightarrow$ headache, Psychiatric,
--- [appears in old patient]

* يفضل أنه لا تقاوم هذه الأدوية للأموال:

* لا يصرف مع أدوية أخرى لتأثير على P₄₅₀

* جميع الأدوية التي تستخدم للـ HCl لا يتم إيقافها بشكل مفاجئ أبداً.

	Cimetidine	Ranitidine	Famotidine
- Anticarcinogenic	✓	X	X
- CVS effect	✓	±	X
- H ₂ Blocking potency	-	+	++
- Duration of Action	3 times daily	2 times daily	Once daily
- Duration of treatment	6 weeks	6 weeks	6 weeks

* إذا تم استخدام دواء 6 أسابيع، فإن الجرعة 200

Third Proton Pump inhibitors \

- like $\Rightarrow$ ① Omeprazole ② lansoprazole ③ Pantoprazole

* MOA $\approx$

- Inhibition of K^+/Na ATPase enzyme irreversibly

- has long duration of Action

- all of these drugs are prodrugs [must be activated
By the HCl] inside the gastric
Gland only.

The most potent drugs, And $\approx$ used for 4 weeks then
4 months.

* C.I $\approx$ Same as H_2 Blocker

* S.E $\approx$ ① Diarrhea

② Inhibits Secretion of intrinsic factor

[$\downarrow$ absorption of B_{12}]

③ Bioavailability changes for other drugs.

[Due to change in stomach acidity]

④ Omeprazole only inhibits the P_{450}

$\rightarrow$ So it has drug interaction with Clopidogrel.

By inhibiting its activation in liver.

⑤ Osteoporosis [Ca need HCl to be absorbed]

Fourth Mucosal Defence Mechanism

like $\Rightarrow$ Sucralfate compounds, Bismuth compounds, PG analogs.

* MOA $\Rightarrow$

① Sucralfate $\Rightarrow$ " Sulfated sucrose + Aluminium "

- Covers the ulcer and protect it.
- less than 5% will be absorbed $\Rightarrow$ Aluminium accumulates in Renal tissue, So It is C.I. for renal failure patients.
- Sucralfate is activated By HCl and it act By Binding to the protein of the ulcerated tissue.
- By its Action it lead to $\Rightarrow$ $\downarrow$ pepsin secretion and $\uparrow$ PG, preventing the irritation of H^+ and HCl.

HCl is not ~~Produced~~ ^{Produced} by PPI $\Rightarrow$ ~~not~~ ^{not} safe *

- Safe in pregnancy.
- The most common side effect is Constipation due to [Al]

② Bismuth compound $\Rightarrow$

- MOA same as Sucralfate.
- help in H. pylori eradication.
- Some of it will absorbed $\Rightarrow$ Pass BBB $\Rightarrow$ Causes encephalopathy.

③ Cebaxolol z

* MOA z

- Stimulate mucus production from the healthy cells
- ↑ healing of the ulcer due to ↑ Blood Flow
- ↑ rate of epithelial turn over.

* S.E z

- May cause salt and water retention

* C.I z

- In edema and hypertensive patients

- If edema occurs due to this drug $\Rightarrow$ Give any diuretic
Except $\Rightarrow$ Spiralolacton Because it has
steroidal structure [prevent competition Between them]

④ Misoprostol z

* MOA z

- Stimulate PG receptors on parietal cell
 $\Rightarrow$ $\downarrow$ cAMP $\Rightarrow$ $\downarrow$ HCl production
- Stimulation of mucus secretion.
- Cause local V.D $\Rightarrow$ ↑ Blood Flow.

* S.E z

- Diarrhea due to ↑ mucous and water secretion

* C.I z

- In pregnancy $\Rightarrow$ lead to uterine contractions

[H. pylori]

* Protocol of treatment for 10 or 14 days

By $\Rightarrow$ P-CAT

① PPI

② clarithromycin

③ Amoxicillin

④ Tinidazole

Second lecture [GERD]

مرض الارتجاع

" Gastroesophageal Reflux Disease "

It is the reflux of Gastric content and acid to the esophagus due to incompetence → which may lead to reflux Esophagitis and transformation to columnar epi.

* Causes \

- ① Diabetes mellitus.
- ② Pregnancy
- ③ Some drugs and disease.

* Symptoms \

mainly morning heart burn.

* Treatment \

- ① Life style modification.
- ② Drugs
- ③ In Sever cases ⇒ Surgery.

* تقسيم مرض الارتجاع إلى نوعين: الارتجاع الحمضي والارتجاع البيلي. وذلك برفع نقطة الارتجاع حوالي 20cm وارتفاع نقطة الارتجاع وتجنب جميع مسببات الارتجاع ولا يتعدى علاج الارتجاع الحمضي.

* Drugs \

First $\downarrow$ HCl By 2

① H_2 Blocker

② PPI

* The best antacid for this patient is **Gaviscon**
which contain 2 - Algenic acid

- NaH_2CO_3

- Mg Trisilicate

- $Al(OH)_3$.

Second Prokinetics drugs -

Drugs which Increase the motility and enhanced evacuation
By acting on the upper GIT.

[Drugs which work on the lower GIT are laxatives]

1) 5HT₄ agonists \

* Mosapride

* Cisapride

* Rifaxipride

MOA $\Rightarrow$ Stimulate Serotonin Receptor type 4,
[Found in GIT and heart]

- Increase Ach in upper GIT $\Rightarrow$ $\uparrow$ motility.

- It may act on 5HT₄ receptor in the heart
and cause $\uparrow$ Q-T interval [torsadogenic]

2) Bethanechol \

- MOA $\Rightarrow$ work on M₃.

- Causing diarrhea.

Non-Selective $\leftarrow$ to all M₃ receptors.

3) Erythromycin \ [Antibiotic]

- MOA $\Rightarrow$ act on motilin Receptor
which found in the upper GIT
lead to $\uparrow$ motility.

- Used in emergency only [Its tolerance is very fast]

4) D₂ Receptor Blockers \

① Metoclopramide :

- MOA ① Block D receptor [D₂ more]

- D receptors are under control of Sympathetic System
So, stimulating them lead to $\downarrow$ motility and
Blocking them $\uparrow$ motility.

- Metoclopramide is Not selective $\Rightarrow$ It Blocks
D receptors peripherally and centrally or CNS.

② Stimulate 5HT₄ receptors $\Rightarrow \uparrow$ Ach
 $\Rightarrow \uparrow$ motility
[Its action on the heart is weak]

③ has antiemetic effect By :

Blocking D₂ receptors of the vomiting center which
is found in area postrema of M.C.

* C.U \

① GERD

HCl ← لا تتركه في المعدة
Selective → لا تتركه في المعدة

② Gastroparesis in D.M

Neuropathy ← Stomach لا يعمل

③ Before endoscopy

In emergency → evacuate stomach

④ Before emergency surgery to prevent
Aspiration Pneumonia

⑤ As Antiemetic drug

* S.E \

Blocks D₂ centrally in z

① Basal Ganglia lead to z

- Extrapyramidal manifestation z

① Dystonia → abnormal facial expression
Reversibly.② Dyskinesia → " " "
Irreversibly.

③ Akathisia

④ Parkinsonism

② Limbic System lead to z

- Altered emotions

③ Pituitary Gland lead to z

↑ Prolactin

② Domperidone z Don't pass BBB

MOA \

① Block D_2 peripherally

② Don't act on $5HT_4$

③ It is also antiemetic

[Block D_2 in area postrema which is outside BBB]

S.E \

↑ Q-T interval

[Torsadogenic]

Date: _____
No: _____



*Third lecture\

...عبدالرحمن...

[Hepatic encephalopathy and esophageal
Varices.]

- Superior mesenteric vein joins the splenic vein forming Portal vein which contain most of Blood of the mesenteric area.
- Chronic liver diseases cause damage or decreasing in the Blood entry to the sinusoid which will cause Increase of Blood pressure in the portal vein.
- Normally the BP in the portal vein is 9 mmHg
portal hypertension mean > 12 mmHg.
- In portal hypertension the Blood goes in other pathways, one of these pathways is left Gastric vein, which has an anastomosis with systemic veins at the lower end of esophagus.
- Increase in portal tension will lead to\
 - ① Dilatation of venous plexus at the lower end of esophagus = Varices.
 - ② Chemical Complications :-
 - Some bacteria in the intestine work on proteins = fermentation and producing NH_3 and other toxic substances like [GABA like] and [Benzodiazepine like mediators]
 - * These substances causes CVS depression.

- Patients with chronic liver disease $\Rightarrow$ Their Blood can't be detoxified in liver, So the Blood shunts to other pathways with these Substances $\Rightarrow$ Reaching Systemic circulation and to the CNS at the end.

* CNS effects of these Substances:

- ① $\text{NH}_3 \Rightarrow$ Brain edema.
- ② GABA like $\Rightarrow$ CNS Depression
- ③ Benzodiazepine like mediator $\Rightarrow$ CNS depression

- The Result is $\Rightarrow$ hepatic coma which is called hepatic encephalopathy or portosystemic encephalopathy.

- So the major two complications of chronic liver disease are \

- ① hepatic encephalopathy
- ② esophageal varices.

* Note \

- $\text{NH}_3 \Rightarrow$ absorbable and cross BBB
- $\text{NH}_4 \Rightarrow$ ionized, can't be absorbed and can't cross BBB.

* Treatment of portosystemic encephalopathy \

1] low protein diet $\Rightarrow$ Decreasing NH_3 production and replace it By vegetable proteins.

2] Lactulose $\Rightarrow$ Not digestible sucrose, It dissolve inside the intestine into $\rightarrow$ Acetic Acid.
 $\rightarrow$ lactic acid.

- These acids will $\downarrow$ pH of the intestine which lead to $\rightarrow$

① Bacterial will eradicated

$\Rightarrow$ lead to $\downarrow$ NH_3 production.

② NH_3 converted to NH_4 which is not absorbed.

③ Shifting of NH_3 found in the Blood to the intestine.

④ Increase water inside intestine $\Rightarrow$ lead to Intestine wash [laxative]

3] Antibiotic $\Rightarrow$ locally work like $\rightarrow$

① Neomycin

② Metronidazole

③ Rifaximin

* Neomycin $\rightarrow$ Not absorbed, work locally

- In 1-2% of patient, absorption will occur and enter to the Systemic circulation causing
 By that ① Nephrotoxicity.

② Autotoxicity.

* Metronidazole work on anaerobic Bacteria

* Rifaximin Non absorbable and work locally.

- These drugs are used as prevention from Complications.

~ Esophageal Varices ~

- These varices will cause severe Bleeding so the treatment will be as the following \

① Fresh Blood Transfusion.

② The patient may develop stress ulcer so we give him PPI in I.V injection.

③ Give him any drug causing V.C in splanchnic area like Vasopressin ~

* Vasopressin act on V_1 receptors which are found in the mesenteric vascular bed, But it is not selective, it will work on V receptors found in the cerebrum and kidney and heart which may cause Myocardial ischemia

* For myocardial ischemia give Nitrate ~ $\rightarrow$
Act as Coronary vasodilator.

* Vasopressin is not used any more, The isomer of it is **Terlipressin or Gylipressin**, It is more selective on Mesenteric vascular bed U.C and $\downarrow$ portal blood flow with out any Systemic vasoconstriction.

* also **Octeatril - Somatostatin** $\Rightarrow$ cause indirect Vasoconstriction

- These drugs will stop bleeding in 20% of patients.

- ④ Endoscopic sclerotherapy
- ⑤ Transjugular intrahepatic portosystemic shunt [TJPSS surgery]

* Prophylactic Treatment \

1] **Non Selective β -Blocker** as propranolol.

- Given in high dose $\Rightarrow \downarrow CO \Rightarrow \downarrow$ Blood flow to the MVB

- Indirect UC By Blocking β_2 receptors.

- [The patient will have sever fatigue]

2] **Nitrate**

- Venous Dilatation $\Rightarrow \downarrow$ Venous return $\Rightarrow \downarrow CO \Rightarrow \downarrow$ Blood flow to MVB.

3] **Metoclopramide** to evacuate stomach faster.

4] **PPI**

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Fourth lecture

2023/10/15

[Management of Constipation]

- Causes of Constipation :-

- ① Chronic idiopathic constipation [CIC]
- ② pregnancy [the uterus compress on the intestine ↓ motility]
- ③ Lack of motility
- ④ Tumors

- Constipation is not serious condition only if this Constipation is with sudden onset and the patient was > 50 years, And Bleeding and weight loss with history of Colon Cancer.

- Treatment :-

* First - Non pharmacological treatment \

- ↑ fibers in diet.
- ↑ fluids
- ↓ Coffee and Tea.
- Exercise

→ 90% will be treated if the cause wasn't obstructive.

* Second pharmacological treatment \

- Laxatives they increase the lower GIT motility and enhanced intestinal evacuation.

Classification of laxative

- ① Bulk laxative
- ② Osmotic laxative
- ③ Irritant laxative
- ④ Lubricant laxative.
- ⑤ chloride channel activator.

1 Bulk laxative \

- ① Bran ② Carboxymethyl cellulose ③ Fibers.

* MOA :

It is not digestible substances $\Rightarrow$ Causes Bulk inside the intestine $\Rightarrow$ Distention in the mucosa of small intestine and colon $\Rightarrow$ stimulate stretch receptor $\Rightarrow$ Local stimulation $\Rightarrow$ $\uparrow$ motility and water secretion.

* SE :

- ① abdominal bloating.
- ② b oligoxine absorption.
- ③ May cause intestinal obstruction

2 Osmotic laxative \

- ① Epsom salts - ~~epididymus~~ ② Lactulose ③ polyethylene Glycol.

- Epsom salts used for rapid evacuation Not in CIC

- It is not digestible, Non absorbable

$\Rightarrow$ $\uparrow$ osmotic pressure inside the intestine $\Rightarrow$ water secretion to the lumen.

* S.E. :

- If there is injury or ulcer in the intestine may lead to absorption of:

① Mg $\Rightarrow$ Arrhythmias.

② Na $\Rightarrow$ Na and water retention.

- Lactulose Acetic acid and lactic acid will
 $\uparrow$ osmotic pressure $\Rightarrow$ water secretion to the lumen

* SE:

abnormal discomferte

- polyethylene Glycol is the same

* SE: hypokalemia

3] Irritant laxative

① Senna

② Castor oil

③ Bisacodyl

* MOA: Cause local inflammation or irritant to
 the mucosa and inhibits Na^+/K^+ ATPase
 This lead to:

① Direct stimulation of the nerve plexus.

② $\uparrow$ local secretion of water.

* SE:

① It is Not used in:

- pregnancy $\Rightarrow$ abortion

- lactating $\Rightarrow$ cathartic baby.

- Menstrual $\Rightarrow$ $\uparrow$ blood flow.

② In chronic use lead to laxative habit
 and cathartic colon.

③ Castor oil has bad taste.

④ Senna $\Rightarrow$ urine discoloration

⑤ Bisacodyl $\Rightarrow$ Severe Gastric irritant

* So it is covered with substance which dissolve only in alkaline medium, So don't use it with antacid.

4] Lubricant laxative \

① Glycerin ② Paraphenol ③ Enema

- Glycerin hygroscopic material $\Rightarrow$ stimulate water secretion $\Rightarrow$ lubrication of anal canal ~ 10 ml

- Paraphenol Non digestible, Coating the fecal matter $\Rightarrow$ Mucosa can't absorb water from the fecal matter.
C.U $\Rightarrow$ In Piles or anal fissures.

- enema for evacuation of the intestine.

5] chloride channel activator \

* Lubiprostone [derivative of PGE₁]

- Used for CIC

- Act on CIC-Cl channels which is found in the apical pole of the columnar cell $\Rightarrow$ $\uparrow$ water secretion.

SE $\Rightarrow$ May cause Nausea and uncomfortable.

↳ The General uses of laxatives \

① CIC

② X-Rays

③ hepatic encephalopathy [lactulose]

④ painful anal fissures and piles

⑤ fastest the secretion of toxic substances.

- General G.I \

① Undiagnosed abdominal pain

② Organic obstruction.

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